use of cDNA encoding the entire constant and variable regions of both the antibody heavy and light chains. Gillies, by contrast, teaches the use of cDNA coding for the variable region of the heavy chain but genomic DNA coding for the constant region of the heavy chain. Dr. Lewis explains in detail in the Declaration filed January 25, 1996, why it would not have been obvious, in view of the art, to make recombinant antibodies according to the present method and the Examiner is urged to reconsider Dr. Lewis' remarks.

In maintaining the rejection, the Examiner refers to page 14, paragraph 2, of the present specification arguing that a method of inserting complete cDNA sequences into expression vectors was known at the time of invention of the claimed subject matter. WO 87/04462 is cited in the indicated portion of the disclosure (copy attached). In the Declaration submitted January 5, 1996, Dr. Lewis discussed at some length why this reference fails to disclose a method of inserting complete cDNA sequences into expression vectors (see paragraphs 5 and 6). Specifically, Dr. Lewis points out that WO 87/04462

> discloses expression vectors containing a recombinant DNA sequence encoding the complete amino acid sequence of a glutamine synthetase. More specifically, the application teaches a method for co-amplifying a recombinant DNA sequence which encodes a desired protein by either (1) co-transforming a host cell with a vector containing a DNA sequence encoding a glutamine synthetase and a vector comprising a recombinant DNA sequence which encodes the desired protein or (2) transforming a host

> cell with a vector containing a DNA sequence encoding a glutamine synthetase and which further contains a recombinant DNA sequence encoding the desired protein …
> The focus of the WO 87/04662 application is on providing the recombinant DNA encoding the complete amino acid sequence of a glutamine synthetase and its use in the construction of expression vectors. There is very little discussion in the application about the DNA encoding the desired protein. In the paragraph bridging pages 9 to 10 of the 04662 application, the applicants state that this DNA can encode tissue plasminogen activator (tPA) or "any other protein, such as immunoglobulin polypeptides (IGs), human growth hormone (hGH) or tissue inhibitor of metalloproteinases (TIMP)." There is no other discussion about the DNA encoding the protein of interest and no discussion of the insertion of complete sequences of both the heavy and light chains of a desired immunoglobulin. There is no discussion in the reference whether the reference "DNA" is intended to refer to cDNA, genomic DNA or the combination of the two. There is no teaching that the light and heavy chains of an antibody could be provided by expressing cDNA encoding the variable and constraint regions of each chain.

(Underlining added.)

It is believed clear from the foregoing that WO 87/04462 does not in fact teach that antibodies can be produced by inserting cDNA encoding both the constant and variable regions of the antibody light and heavy chains into an expression vector under the control of expression signals, transfecting a host cell with a vector and then culturing the host under protein-producing conditions.

As for the Examiner's assertion that there is no evidence that Gillies et al actually removed the 3' untranslated sequence,

attention is directed to the second page of Gillies et al, right hand column, last paragraph entitled "Expression Vector Construction". There, it is clearly stated that:

> since the cDNA sequences also contain a poly A tract at their 3' ends as a result of the cloning process we chose to insert the GF4/1.1 cDNAs into vectors that have either had these sequences removed (in the case of the light chain) or utilised fusion of the heavy chain cDNA to a Cy3 region in its genomic configuration … .

(Underlining added.)

Furthermore in the "Discussion" section of Gillies et al, second paragraph, it is stated that:

> our approach of fusing cDNA and genomic sequences is possible in the present case because the cDNA and genomic region encoded the same y3 isotype. Another approach would be necessary if the isotype was to be changed: either the use of the genomic V region or some other method of linking the variable portion of the h-chain cDNA to a different constant region. We have recently described such a system whereby short oligonucleotide linkers were used to provide splice donor sites at the end of the variable region of the Ig cDNA so that they could be used in conjunction with the Ig constant regions genes…".

Under the "Experimental Protocol" and "Expression Vector Constructions" sections, Gillies et al again describe fusion of cDNA to genomic DNA and removal of poly A.

In view of the above-referenced teachings, it is believed clear that Gillies et al did actually remove the 3' untranslated sequence.

The Examiner further contends that the claims fail to recite the requirement that the poly A tail is introduced into the construct. Respectfully, the poly A tail is part of the cDNA sequence and thus is inherently present. The invention differs from the art in that the art teaches removing the poly A tail. This distinction is captured by the claim term "entire" i.e. including poly A.

Claims 3 and 6 remain rejected under 35 USC 103 as allegedly being obvious over Gillies et al in view of Foung et al and Ehrlich et al. This rejection is again traversed.

The inadequacies of Gillies et al are discussed above, that discussion being relevant here (note also comments above relating to WO 87/04462). The teachings of the secondary references cited by the Examiner are not sufficient to overcome these deficiencies. Neither Foung nor Ehrlich et al teach or suggest any method for producing recombinant antibodies, much less that a recombinant antibody could be produced by obtaining the cDNA encoding the entire constant and variable regions of each of the heavy and light chain of the antibody. Accordingly, reconsideration is again requested.

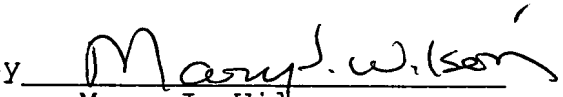
Claim 11 remains rejected under 35 USC 103 as allegedly being obvious over Gillies et al in view of Larrick et al. Again, the deficiencies of the Gillies et al reference, as set forth above, are equally applicable to this rejection. The secondary reference does not compensate for the deficiencies of

the primary reference. As indicated above, Gillies et al teach that it is necessary to use genomic DNA as the source for part of the DNA encoding the constant region of the antibody chain. Larrick et al do not address this issue. They teach a method of amplifying human monoclonal antibody variable region genes using PCR and a mixture of upstream primers corresponding to the leader sequence and one downstream primer designed from the conserved nucleotide sequence of the constant region. The reference does not teach any primers which would enable the amplification and cloning of the entire gene including both the constant and variable regions. The combined teachings of these references do not teach or suggest the method set forth in claim 11 of this application. Accordingly, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE, P.C.

By 
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